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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/665,350	09/18/2000	Avi Ashkenazi	10466/14	8200

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EXAMINER	
CHERNYSHEV, OLGA N	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/665,350	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-46 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-46 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 08, 2004 has been entered.

Response to Amendment

2. Claims 39-46 and 50 have been amended and claim 47 has been cancelled as requested in the amendment filed on October 08, 2004. Claims 39-46 and 49-51 are pending in the instant application.

Claims 39-46 and 49-51 are under examination in the instant office action.

3. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed on October 08, 2004 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Objections

6. Claims 39-44 are objected to because of the following informalities: claims 39-44, as amended, contain recitation "or" in section (c), which cannot be construed as a reference to an isolated polypeptide within the claimed group. Appropriate correction is required.

7. Claims 39-43 are further objected to because of the following informalities: claims 39-43 recite the limitation "wherein, the nucleic acid" in section (d), which appears to have a misplaced coma. Appropriate correction or clarification is required.

Claim Rejections - 35 USC § 101

8. Claims 39-46 and 49-51, as amended, stand rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility for reasons of record in section 7 of Paper No. 19 and in section 6 of Paper mailed on November 25, 2003. Briefly, the instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose a specific biological role for this protein or its significance to a particular disease, disorder or physiological process, which one would wish to manipulate for a desired clinical effect.

At the middle of page 13, Applicant summarizes case law on utility rejections and refers to the Utility Examination Guidelines. Applicant's review of the issue of utility, the case law that has been cited and the holding that is found in that case law are not disputed. The only point of disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility.

The instant claims are drawn to isolated and chimeric PRO 187 polypeptides. The instant specification disclose the data regarding significant amplification of DNA sequences encoding PRO187 in lung and colon tumors, which supports practical utility of the PRO 187 DNA. As fully explained in the previous office actions of record, the increased copy of DNA does not provide a readily apparent use for the polypeptide PRO 187 itself, for which no information regarding critical level of expression symptomatic of cancer, specific biological activity or role in cancer is disclosed.

At page 14 Applicant argues that "it is well-understood in the art that, in general, DNA copy number influences gene expression" and refers to articles by Orntoft et al., Hayman et al. and Pollack et al. as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. This argument has been fully considered but is not considered to be persuasive for the following reasons.

Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. However, Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region, which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO 187 in the

instant specification. That is, it is not clear whether or not PRO 187 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft et al. is not clear.

Further, Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides.

With respect to Pollack et al. publication, Applicant characterizes it as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, these publications do not appear to support the specification's assertions that the claimed PRO 187 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics.

The Declaration of Polakis under 37 CFR 1.132 filed on October 08, 2004 is insufficient to overcome the rejection of claims 58-65 and 68-70 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons.

The Declaration provides additional support to Applicant's statement that increase in the level of mRNA is predictive of corresponding levels of the encoded protein. However, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO 187 in tumor samples as compared to normal samples. Only gene amplification data were presented. Therefore, the declaration is insufficient to overcome the rejection of the instant claims 58-65 and 68-70 because it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not to gene amplification levels and polypeptide levels. Furthermore, the instant specification, as filed, provides data showing a very small increase in DNA copy number. According to the information provided in Table 9, PRO187 DNA was found to be expressed at the level from 1.67 to 4.05 units in 6 out of 17 samples of lung carcinoma, which is in 35% of all cases. Further, according to Table 9, PRO187 DNA was found to be expressed at levels from 1.01 to 3.56 units in 10 out of 17 samples of colon cancer, which constitutes 59% of cases. There is no evidence regarding whether or not the PRO 187 mRNA or polypeptide levels were also increased in these tumor samples. Since the instant claims are directed to PRO 187 polypeptide, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number approximately in half of the examined cases would be considered by the skilled artisan to be predictive of increased in mRNA and polypeptide levels. Additionally, article by Pennica et al. (PNAS, 1998, Vol. 95, pp.14717-22) shows a lack of correlation between gene (DNA)

amplification and elevated mRNA levels (see page 14721, first column, for example). Also, Konopka et al. was cited in the previous communication of record as evidence showing lack of correlation between gene amplification and increased polypeptide levels.

Thus, providing how small was the increase of the PRO 187 DNA copy number, and in view of the evidence provided by publications of Pennica et al. and Konopka et al., one skilled in the art would reasonably conclude that a small increase in gene copy number would not significantly correlate with increase in polypeptide levels. One skilled in the art would have to resort to further research to determine whether or not the PRO 187 polypeptide levels are increased significantly in the tumor samples. Such further research requirement makes it clear that the asserted utility is not yet in currently available form. It is a matter of law that the claimed invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention. Finally, it is noted that the Declaration of Polakis does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research, 2, pp. 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors

compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

At page 16 of the Response, Applicant submits that "[e]ven assuming *arguendo* that, there is no correlation between gene amplification and increased mRNA/protein expression for PRO 187, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would still have a credible, specific and substantial utility". Applicant refers to the Declaration of Ashkenazi, which explains that a practitioner treating a cancer patient and knowing that PRO 187 DNA of cancerous samples is amplified but PRO 187 polypeptides expression is not changed, would adjust a treatment protocol by not treating the patient with agents that target that gene product.

The Declaration of Ashenazi under 37 CFR 1.132 filed on October 08, 2004 is insufficient to overcome the rejection of claims 39-46 and 49-51 based upon §§ 101 and 112 as set forth in the last Office action because the Declaration provides only Dr. Ashenazi's own conclusions and no references to scientific reasoning or any evidentiary clinical support (see *Meitzner v. Mindick,* 549 F.2d. 775, 782, 193 USPQ 17, 22 (CCPA 1977), "Argument of counsel cannot take the place of evidence lacking in the record").

Finally, article by Hanna et al. appears to be contradicting Applicant's statement that "[e]ven when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and more effective treatment of it" (middle at page 17 of the Response). Specifically, at page 1, bottom of the second column of Hanna et al. article, it is

stated "In general FISH and IHC results correlate well. However, subsets of tumors are found which show discordant results; i.e., protein overexpression without gene amplification or lack of protein overexpression without gene amplification. The clinical significance of such results is unclear" (emphasis added). Thus, according to the quoted document of Hanna et al., there appears to be no support for significance of correlation of amplified DNA *versus* overexpressed protein with respect to adjustment of regime of treatment of cancer patients.

Therefore, for reasons of record in previous office communications of record and also reasons of record in the instant office action, the instant rejection is maintained.

Claim Rejections - 35 USC § 112

9. Claims 39-46 and 49-51 stand rejected under 35 U.S.C. 112, first paragraph for reasons of record in section 8 of Paper No. 19 and in section 7 of Paper mailed on November 25, 2003. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. Claims 39-43 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record in section 9 of Paper No. 19 and in section 8 of Paper mailed on November 25, 2003.

Applicant submits that because the claims now include recitation regarding proteins being encoded by a nucleic acid amplified in lung or colon tumors, the instant claims now satisfy the written description requirement. This argument has been fully considered but is not deemed

to be persuasive because, as fully explained in the previous office actions of record, the instant specification fails to describe the entire genus of the claimed polypeptides, which are 80%, 85%, 90%, 95% and 99% identical to an amino acid sequence having SEQ ID NO: 23, which are encoded by a nucleic acid amplified in lung or colon tumors. There is no disclosure of complete structure of the claimed polypeptides, or other relevant identifying characteristics (physical and/or chemical and/or functional characteristics coupled with a known or disclosed correlation between function and structure), or representative number of species for the claimed genus, except for one polypeptide of SEQ ID NO: 23. Therefore, the claims are directed to subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (571) 273-0870. Official papers should NOT be faxed to (571) 273-0870.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.
Primary Examiner
Art Unit 1646

December 2, 2004